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# Identification and management of pleural effusions of multiple aetiologies

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**Purpose of review:** Historically, pleural effusions have been attributed to a single cause. There is growing recognition that a substantial proportion of pleural effusions may have more than one underlying cause. The purpose of this review is to summarise recent findings regarding the diagnosis and treatment of effusions secondary to more than one aetiology.

**Recent findings:** A recent prospective study identified that 30% of pleural effusions had more than one underlying aetiology. With a rising prevalence of cardiovascular and malignant disease, the incidence of the complex pleural patient is increasing. The use of biomarkers, including Pro-BNP, have been suggested as a way of identifying contributing disease process.

**Summary:** Understanding that there are potentially concurrent causes to a pleural effusion is vital in establishing the diagnoses of multiple underlying aetiologies. New diagnostic pathways, with increasing use of biomarkers, will be required to identify the complex pleural effusion. Further studies on whether the targeting of separate aetiologies improves outcomes will help develop future management strategies.

## Key Points:

- Pleural effusions secondary to multiple aetiologies are common, accounting for 30% of all unilateral effusions.
- Reaching the diagnoses can be difficult, and requires a high index of suspicion
- Serum Pro-BNP is useful in identifying a cardiac component, with a serum value of >1,500pg/ml suggestive of a cardiac effusion.
- Further disease-specific biomarkers will be in key in developing a diagnostic algorithm

## Introduction

The incidence of malignant and cardiovascular disease is increasing (1, 2), and with it, the prevalence of the complex pleural patient. Patients often present with established comorbidities, such as cancer and benign lung disease, together with risk factors for cardiovascular, renal and metabolic disease, which all can interact with each other at the pathophysiological level(3). This can make it difficult for the physician to identify the predominant cause of the patients' symptomatology.

Whilst traditionally, a pleural effusion has been attributed to a single aetiology, there has been increasing recognition it may be a result of several interplaying disease processes. A recent study has supported this, demonstrating that 30% of the patients studied with a unilateral effusion had more than one underlying aetiology (4). This is likely to be underappreciated due to current diagnostic algorithms and tools which are not designed to identify multiple causes(5). The binary classification of transudates and exudates also encourages the notion that the effusion has a singular cause.

Recognition that multiple processes may be responsible and that establishing one diagnosis does not exclude other causes(6) is key in forming a comprehensive diagnosis. The identification of certain contributory causes clearly warrants changes in management approach, whilst in others the benefits are less clear(4).

New diagnostic algorithms, likely with an increased role of biomarkers, will be required to identify and manage the complex pleural effusion. This article will explore possible diagnostic approaches and subsequent treatment options for pleural effusions secondary to multiple aetiologies.

## Moving on from the traditional approach

Unilateral pleural effusions are classically felt to result from a singular disease process, despite having over 60 possible causes. The pathogenesis and subsequent clinical evaluation of pleural effusions is typically divided into transudative (increased hydrostatic pressures, decreased oncotic forces or decreased intrapleural pressures) or exudates (increased capillary permeability and impaired lymphatic drainage) (7) using the three part Light criteria. However these processes do not need to be mutually exclusive and it is possible for more than one to occur.

There is no specific test to determine the underlying cause of an effusion and the diagnosis is typically reached after a step-wise approach of investigations, including clinical evaluation, pleural fluid biochemistry, imaging techniques and possibly pleural biopsy. This subcategorises the effusion: exudate vs transudate, lymphocytic vs neutrophilic, malignant vs non-malignant. This binary approach leaves little room to consider an additional cause behind the pleural effusions.

This approach has been challenged by increasing recognition that a substantial proportion of pleural effusions have dual aetiology. On the background of case studies detailing pleural effusions with multiple contributory factors(6), a prospective study of 126 patients with undiagnosed unilateral pleural effusions determined that 30% (38/126) had more than one cause to their effusion(4). Heart failure was the most common secondary cause, accounting for 51% (21/41). Pleural infection and malignancy contributed 20% (8/41) and 17% (7/41) of secondary causes respectively. Malignancy, however, was the commonest primary diagnosis, at 46% (58/126), and 21% (12/58) of patients with

malignancy had more than one apparent causes. This was not uniform amongst cancer subtypes, with 41% (7/17) of lung cancer malignant pleural effusions (MPE) thought to have a contributory cause.

### The complex pleural effusion

Identification of multiple aetiologies begins with recognising several key principles:

1. **Multiple** processes may be responsible (i.e. avoid causal oversimplification)
2. Establishing one diagnosis does not **exclude** other causes(6)
3. Pleural effusions, and their possible aetiologies, can **change with time** and the initial cause of the effusion (i.e. infection) may exacerbated a further cause (i.e. atrial fibrillation leading to decompensated heart failure)
4. Certain causative factors frequently occur together, as **coupling factors**, exacerbating one another (i.e. hypoalbuminaemia in malignancy).

Consider these two cases:

#### **Case 1: Malignant Pleural Effusion with parapneumonic and hypoalbuminaemia**

A 76 year old gentleman presented with dyspnoea, febrile episodes ( $>38^{\circ}\text{C}/100^{\circ}\text{F}$ ) and with large left pleural effusion and consolidation on chest radiograph. He had been under investigation for a solitary pulmonary nodule. Blood tests demonstrated raised inflammatory markers (CRP 142mg/L), hypoalbuminaemia (albumin 16g/L) and NT-proBNP of 475pg/ml. The fluid biochemistry demonstrated exudate, with high LDH 2467U/L, low glucose 1.7mmol/L and pH 7.32. Pleural cytology demonstrated adenocarcinoma (TTF-1 positive), consistent with lung primary. CT demonstrated consolidation of left lower lobe, bronchial wall thickening and a left unilateral effusion with no proximal mass evident. The diagnosis was malignant pleural effusion with secondary and exacerbating causes of simple parapneumonic effusion and hypoalbuminaemia. He was treated with antibiotics and chest tube insertion and referred to lung MDT.

#### **Case 2: Cardiac effusion with complicated parapneumonic effusion**

A 93 year old lady, with previous clinical diagnosis of heart failure, presented with dyspnoea, in fast atrial fibrillation and evidence of fluid overload. Chest radiograph demonstrated bilateral effusions and right sided consolidation. Her blood results demonstrated a CRP of 264mg/L, albumin 28g/L, Na 122mmol/L, WCC  $18.8 \times 10^9/\text{L}$  (neutrophils  $14.4 \times 10^9/\text{L}$ ). Pleural aspiration of the right effusion demonstrated a neutrophilic predominant cell type effusion with low pH (6.98), but, interestingly, with low pleural protein and LDH level of 24U/L and 328U/L respectively (serum protein 55g/L and serum 798g/L). Echocardiogram demonstrated signs of right heart failure (dilated RA, PASP 60mmhg, and dilated LA, with persevered LV function). NT-proBNP was  $>3000\text{pg/ml}$ . The diagnosis with pneumonia with complicated parapneumonic effusion precipitating atrial fibrillation, resulting in decompensated heart failure. She was treated with antibiotics, anti-arrhythmic medication, diuresis and thoracentesis.

A suspicion of concurrent disease processes should prompt a robust diagnostic workup(4). The first step is clinical history and exam. Clinical exam should elicit signs of fluid overload and organ dysfunction (heart, renal and liver failure) in particular. Evidence of fluid overload is an indication of treatment with diuretics first (8). However, it must be noted that 15% of malignant pleural effusions are bilateral effusions (9) and conversely 27% of effusions from CHF are unilateral(10).

Analysis of pleural fluid by the Light Criteria will help identify the main driving cause of the pleural effusion. The strengths and limitations of the Light criteria are well-documented. It is highly weighted towards sensitivity in identifying exudative processes and suffers in sensitivity in identifying transudates. The can lead to over-diagnoses of transudates as exudates, particularly if the patient is on diuretics. Additional techniques, for example serum-pleural albumin gradient ( $>1.2\text{g/dl}$ ) improves its specificity and sensitivity (11). Recognising both these limitation and that the Light criteria was not designed to detect pleural aetiologies of multiple causes does not diminish its usefulness. A nuanced usage of the criteria, combined with clinical acumen, enables the clinicians to determine the primary driver of the effusion, without losing focus that there may be more than one cause.

A cell differential is usually performed to classify the effusion as neutrophilic, lymphocytic, eosinophilic or mixed. Whilst, neither category is specific to a particular aetiology, a neutrophilic predominant cell type is suggestive of an acute inflammatory cell type, whilst a lymphocytic predominant cell type typically represents an more chronic process, for example malignancy or TB. Rapid processing of a pleural cell differential can be useful to differentiate between complex parapneumonic effusions and malignant effusions.

Pleural fluid flow cytometry (lymphocyte subset analysis) can be used to be diagnose haematological malignancy (8) and there may be a role in its used in an undiagnosed lymphocytic predominant pleural effusion, particularly if the patient has a history of haematological cancer (based on local unpublished work).

Pleural fluid is usually sent for cytology to examine for presence of malignant cell. However it is well recognised it has a high rate of false negative, with only 60% of malignant pleural effusions demonstrating malignant cells. Pleural histology, obtained via percutaneous or thoracoscopy biopsy is valuable in investigating for malignancy, though the frequent finding of non-specific pleuritis is often not useful.

## Biomarkers

Biomarkers are increasingly used to help establish the underlying aetiology in the complex patient(3). Whilst there is a lack of disease-specific biomarkers available at present, there are several which can be useful (see table 1).

Table 1: Use of common Biomarkers in pleural disease				
Biomarker	Indication	Value	Sensitivity	Specificity
Serum Mesothelin(12)	?Mesothelioma	$>2\text{nmol/l}$	47%	96%
Serum NT-proBNP(13)	?CHF	$>1500\text{pg/mL}$	95%	95%
Pleural fluid ADA(14)	?TB	$>40\text{U/L}$	92%	90%
Serum CRP (+neutrophilic effusion)(15)	?Parapneumonic effusion	$>45\text{mg/L}$	64%	92%
ADA: Adenosine Deaminase; CRP: C-reactive protein; CHF: Congestive heart disease; TB: Tuberculosis.				

NT-ProBNP, a neurohormone secreted by stretched cardiomyocytes in response to increase atrial pressure, is used as a biomarker to detect likelihood of heart failure. In patients with pleural effusions, its sensitivity and specificity have been found to be 94% with a likelihood ratio (LR) positive of 15.2 and LR negative of 0.06 in meta-analysis (13). Though differing values of NT-proBNP were used, 6 studies used values around 1,500pg/ml as the cut off, with a pooled sensitivity and specificity of 95% and 95% respectively(13). Therefore, a cut-off of NT-proBNP levels of greater than 1,500pg/ml argues convincingly for heart failure in patients with pleural effusions (16).

The prospective study by Bintcliffe et al on unilateral effusions examined the utility of NT-proBNP in establishing the diagnosis of heart failure. This study demonstrated a lower sensitivity and specificity for primary diagnosis of heart failure (76% and 74% respectively) than reported elsewhere. This was likely related to low-pretest probability of heart failure in these patients. It was more useful in detecting the contribution of heart failure to the aetiology of pleural effusion, with a sensitivity and specificity of 79% and 88% respectively. BNP levels can be influenced by other comorbidities in the complex patient. It is recognised that renal impairment increases the level of BNP and NT-ProBNP by 20.6% and 37.7% for every 10-mL/min/1.73 m<sup>2</sup> (0.17-mL/s) reduction in estimated GFR(17). BNP specificity, for a given cut off, is widely recognised to decrease with age, as the level of BNP increases with age(18). This does pose difficulties when deciding the cut-off level of BNP, as increasing the cut-off level to increase specificity will decrease sensitivity(18).

C-reactive protein (CRP) is an acute phase reactant protein that is raised in systemic inflammation. It can be used to suggest an infectious aetiology in pleural effusions, particularly when combined with other tests. The combination of neutrophilic pleural fluid and a CRP >45mg/l is highly suggestive of pleural infection (LR =7.7) (15). However, CRP is often significantly elevated in malignancy as well.

The biomarker, procalcitonin, is recognised as a marker of bacterial infection, and has been used to determine length of antibiotics in bacterial chest infections(19). There have been conflicting results on its use in differentiating between parapneumonic and non-parapneumonic effusion (20-22) and it is not routinely used.

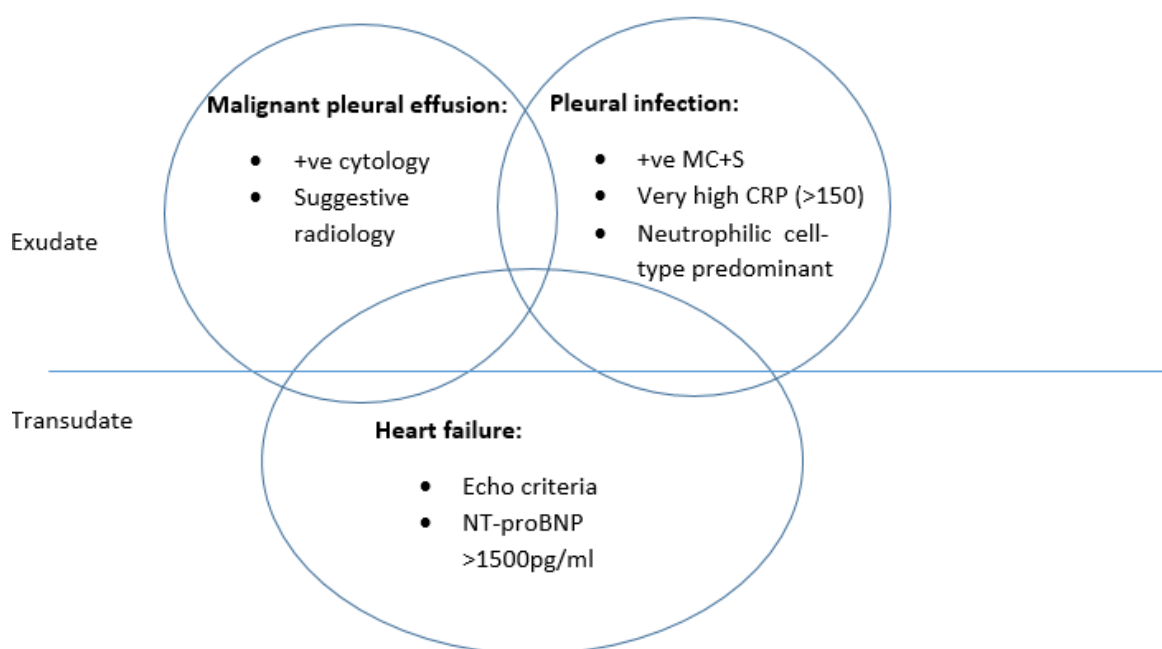
Tumour markers have traditionally had a limited role in the diagnosis of pleural effusions. Tumour markers (carcinoembryonic antigen (CEA), cancer antigen 125 (CA 125), carbohydrate antigen 15–3 (CA 15–3), and cytokeratin 19 fragments (CYFRA 21–1)) have low individual sensitivity in diagnosing malignancy in pleural effusions (<30%), and when combined their sensitivity, at 50%(23), is lower than that of pleural cytology. Mesothelin, as a diagnostic marker for mesothelioma, has a high specificity but poor sensitivity in differentiating between high risk controls(12). So whilst a high mesothelin level should prompt further investigation, a low measurement is not reassuring.

There are several biomarkers useful when a particular disease process is suspected. Triglycerides (TG) and chylomicrons are useful in determining the presence of chylothorax or pseudochylothorax, with over 85% of patients with a chylothorax having a TG levels >110mg/dl and <3% will have a value <50mg/dl(24). Amylase, whilst suggestive of an effusion caused by pancreatitis, or oesophageal perforation, the commonest cause of a high amylase is malignancy(25) and the routine measurement of pleural fluid amylase has not been found to be helpful in achieving a diagnosis(26). Pleural Antinuclear Antibody (ANA) in pleural strongly supports the diagnosis of lupus pleuritis(27). Adenosine Deaminase (ADA) is useful in determining the presence of tuberculosis and been shown to be more sensitive and specific (92% and 90% respectively(14)) than the microbiology of both in sputum and pleural fluid (28) (29). However, other diseases can demonstrate high pleural fluid ADA levels, most commonly

parapneumonic effusions, empyema and lymphomas, with one study demonstrated high ADA levels in 44%, 70% and 57% of these conditions respectively(30).

The biomarkers that are available are mainly of use in diagnosing the uncommon causes of pleural effusions. It is unclear how sensitive, specific and cost-effective a panel of these biomarkers would be in reaching final diagnoses(5). NT-Pro-BNP is a proven biomarker in heart failure and we would suggest that a result of >1500pg/ml should prompt further investigation for heart failure as a contributory cause. A raised CRP, particularly in the presence of a neutrophilic effusion, is suggestive of a parapneumonic process.

Features suggestive of more than one aetiology:



**Figure 1: Venn diagram of common interplaying pathophysiologies of pleural effusion**

#### Raised NT-ProBNP

The study by Bintcliffe et al (31) found that over half of the secondary contributory diagnoses were heart failure. As discussed above, NT-ProBNP has been shown to be an effective biomarker for diagnosing heart failure in pleural disease. Whilst, its sensitivity and specificity is lower when applied indiscriminately to all pleural effusions, when there is a suspicion of heart failure, a value of greater than 1500pg/ml should prompt investigation with an echocardiogram.

Conversely, with approximately 5% of malignancy identified as transudates(32), a transudate with features suggestive of another cause (i.e. CT features, low pH, raised CRP) should raise the suspicion of more than one underlying process (see Fig 1).

### Hypoalbuminaemia

Low albumin is not uncommon in patients with pleural infection and malignancy and is a marker of severity in pleural infection(33). Whilst the presence of mild hypoalbuminaemia in isolation is not thought to cause pleural effusions(34) and is unlikely if albumin  $\geq 18$  u/L, in the presence of other disease processes (see Fig. 2) it could be a contributory cause and nutritional supplementation should be optimised.



**Figure 2: Pleural effusion in patient with hepatomegaly and cardiomegaly.**

### Other strategies:

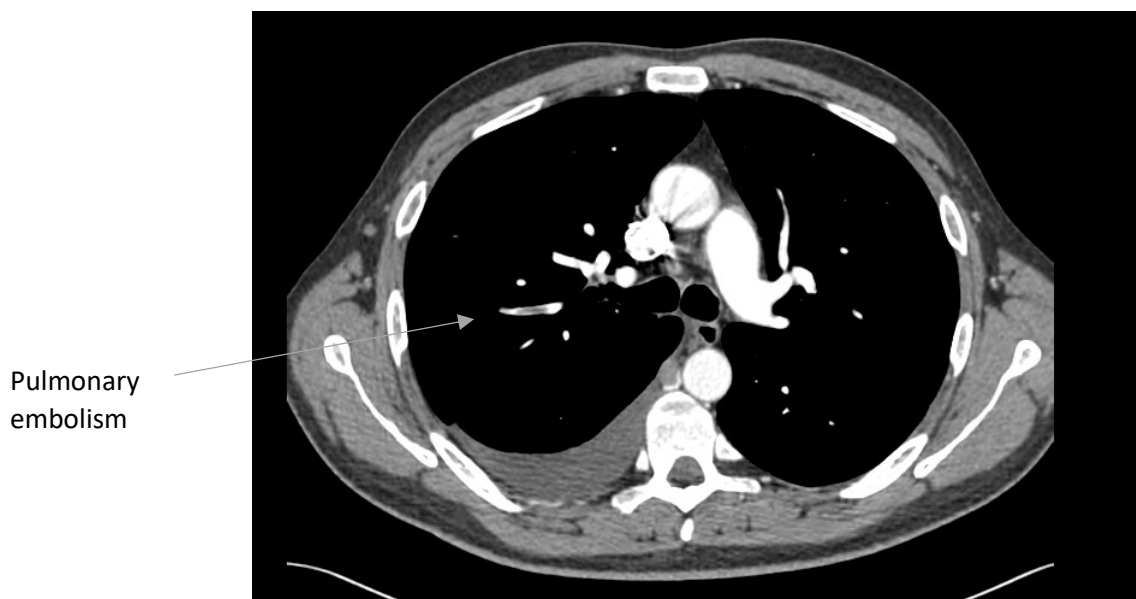
#### Dual Phase CTPA

The clinical diagnosis of pulmonary embolism (PE), particularly in the presence of a pleural effusion, can be difficult(35). A prospective trial investigating the incidence of PEs in consecutive patient with a unilateral effusions, with a dual phase CTPA (35), found the incidence of concurrent PEs was low (6.4%) and in no cases was it felt to be the leading cause of the effusion. PE was only clinically suspected in



one case. It was more frequent (9.8%) in patients who were subsequently diagnosed with pleural malignancy. Malignancy is an independent risk factor for venous thromboembolic disease (VTE) (36), increasing the overall risk 7-fold in patients with cancer, and 22 fold in patients with lung cancer (37). This study demonstrates that PEs are uncommon in unilateral effusions, however if it does occur, it is frequently associated with malignancy (35).

A dual phase CT, incorporating CTPA and pleural phase imaging may allow both the investigation of the pleural and exclusion of PE, and would be recommended if pleural malignancy is suspected. A CTPA could also be considered if breathlessness does not improve post aspiration or there are features on fluid analysis suggestive of PE-related effusion (high haemocrit, neutrophilic). Conversely, the pleural effusion secondary to a pulmonary embolism are typically small (see Figure 3), and a larger effusion should prompt investigation for a concomitant cause (31)



**Figure 3: Pulmonary embolism and malignant pleural effusion**

#### [Pleural manometry in the unexpandable lung](#)

Understanding the pathophysiology of the unexpandable lung can be used to demonstrate dual pathology in pleural disease (38). Chopra et al demonstrated this, in a patient with a pressure/volume curve consistent with entrapped lung, but with a transudative effusion, they could demonstrate an effusion of mixed aetiologies (38). Whilst this will be of limited use in the majority of patients, it is a good example of the use of basic science in making the diagnosis in a complex patient.

#### [Management](#)

The identification of one or more contributory cause to a pleural effusion should prompt consideration for change of management pathway. For some disease processes, there would be strong justification of additional management. The identification of concurrent thromboembolic disease, pleural

infection, or malignancy should prompt instigation of appropriate management. The presence of heart failure or hypoalbuminaemia, may act as 'coupling factors' for the common exudates (malignancy and infection), promoting more rapid accumulation. And the use of diuretics in CHF and treatment of hypoalbuminaemia should be considered to decrease rate of fluid re-accumulation. However, it has not been established that optimising organ dysfunction, for example CHF with malignant pleural effusion, would lead to improved outcomes (4). This would need to be subject to future interventional control trials. The identification of more than one cause may have an effect on prognosis. A study by DeBiasi demonstrated that the mortality of patients with multiple benign aetiologies was higher (55% 1 year mortality) than those from single benign aetiology(39), and a high serum NT—pro BNP has been shown to be independently associated with poor prognosis in patients with malignant pleural effusions(1).

## Conclusion

With an aging population and increasing rates of congestive heart disease and malignant pleural disease, it is likely there will be an increase in the proportion of effusions caused by multiple aetiologies. Understanding that there are potentially concurrent causes to a pleural effusion is vital in establishing the diagnoses. Disease-specific biomarkers will be in key in developing a diagnostic algorithm in the complex pleural patient and further work will build upon this. Future studies examining the efficacy of treating multiple underlying causes of a pleural effusion, i.e. concurrent cardiac effusions with malignant pleural effusion, will help develop management pathways.

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